Chapter

Contribution of Biomedical Equipment Management to Better Management of Sickle Cell Disease in Africa

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Abstract

Sickle cell anemia is a serious disease with manifestations and complications that directly affect the patient's quality of life and his entourage. This is not a shameful disease on the contrary; it is linked to a mutation that arose for us to defend against severe forms of malaria. It is due to the so-called selective pressure that has enabled AS carriers to resist severe forms of malaria. This advantage explains among other things why, although cosmopolitan, sickle cell disease predominates in Africa and its geographical distribution is superimposed on the malaria one. In the Democratic Republic of the Congo (DRC), it is estimated that there are 25–30% heterozygous healthy carriers (AS) and about 50,000 homozygous newborns (SS) each year, equating to 2% of newborns. Therefore, an effective medical care is very indispensable. The management of any pathology implies the appropriate choice of techniques and technologies. Unfortunately, very often in sub-Saharan countries, there is a lack of global strategy to providing effective solution. The choice of equipment performed after an objective needs analysis enables to optimize the acquiring process, to ensure the quality of reported results, and to provide more accessible costs to target populations that are generally poor. Biomedical engineers may enhance health by assessing and managing health technologies.

Keywords: sickle cell anemia, project management, biomedical equipment, planning

1. Introduction

By way of introduction, the quotation below significantly translates the problem of sickle cell disease both in the Democratic Republic of the Congo and in most countries of sub-Saharan Africa:

> *"Sickle cell disease is a genetic inherited disorder where hemoglobin (Hb) normal A (HbA) is replaced by another abnormal, HbS."*

Sickle cell anemia is a *serious disease* with manifestations and complications that directly affect the patient quality of life and his entourage. *This is not a shameful*

disease contrary; it is linked to a mutation that arose for us to defend against severe forms of malaria. It is due to the so-called *selective pressure* that has enabled AS carriers to resist severe forms of malaria. This advantage explains among other things why, although cosmopolitan, sickle cell disease predominates in Africa and its geographical distribution is superimposed on the malaria one.

There are *four major outbreaks of sickle cell disease* based on genetic markers called haplotypes: Arabo-Indian, Beninese, Senegalese, and Central African or Bantu. Among Bantu haplotype carriers, the clinical expression of the sickle cell disease is more severe because of, among other things, the relatively low rate of the fetal hemoglobin (HbF) and other genetic factors.

According to WHO estimates, approximately 300–500,000 children are born each year with hemoglobinopathy; 80% of them are born in developing countries, particularly in Africa. The sickle cell anemia is a hemoglobin disorder most common in Africa, where every year about *200,000 newborns with sickle cell disease* are diagnosed and 80% will not reach the age of 5 years.

In the Democratic Republic of the Congo (DRC), it is estimated that there are 25–30% heterozygous healthy carriers (AS) and about *50,000 homozygous newborns (SS) each year*, equating to 2% of newborns [1].

Sickle cell disease is particularly common among people from sub-Saharan Africa, India, Saudi Arabia, and Mediterranean countries. Migration has increased the frequency of the offending gene in the Americas. In parts of sub-Saharan Africa, sickle cell disease affects up to 2% of newborns. More broadly, the prevalence of sickle cell disease (healthy carriers that inherited the mutant gene from only one parent) in equatorial Africa is 10–40%, compared to only 1–2% on the coast of North Africa and less than 1% in South Africa. This distribution reflects the fact that the sickle cell trait confers an advantage in terms of survival against malaria and that the selection pressure due to malaria has made the mutant gene more frequent, especially in areas with high malaria transmission. In West African countries such as Ghana and Nigeria, the rate of trafficking is 15–30%, while in Uganda, where marked tribal variations are observed, it is 45% among the Bahamas of west of the country [2].

2. Problems of financing of health systems and their corollary in the DR Congo

2.1 Deficit in sources of health-care funding

A country's problem of access to health care depends on its ability to finance the required health systems. This presupposes that the country concerned can offer structures, viable infrastructures, and competent personnel. However, low-income countries are struggling to find adequate budget balances to effectively meet the ever-growing health needs of their populations [3], and this is the case of the DR Congo and many other countries in sub-Saharan Africa.

Indeed, the current sources of financing useful for universal health coverage are essentially public expenditure, donor funding, and compulsory contributions to social health insurance [4]. Since under current conditions household contributions to health care remain relatively low, with a few exceptions when community initiatives are organized [5] or when the state is effectively involved, only two sources are secure: public spending and donor funding.

With regard to public expenditure, the state budget is low, often well below Abuja's commitments (15%) [6]. In 2013, for example, the Congolese state allocated only 4.3% of its budget to health, while all projections for spending in 2020 are below 3%. Worse still, this state contribution has only decreased from 2013 to date.

It just so happens that a large part of the financing of the health system relies heavily on donor funding. And in order to cover all needs, donors will theoretically have to continually increase their contribution in proportion to the decrease in the state budget.

But is such a hypothesis sustainable? Logically, the answer is negative, since donors cannot set themselves up as substitutes for failing health systems. Indeed, the study of the financing mechanism supported by the World Bank Group shows that "the health sector in the DRC suffers from several ills: low budget allocation; excessive household expenditure; dependence on external financing; available resources are poorly spent; budget execution is weak; governance problems; and the decentralization process is partly theoretical." [7] The same study shows that a decrease in external financing is observed from 2017, just as the projections predict that the deficit financing observed since 2019 will have to continue until 2030.

2.2 Attempt to address the funding gap for the management of sickle cell disease

In the specific case of the management of sickle cell disease, are there other ways of compensating for this financial situation?

The first way already present in the field is that of the actions of charitable associations. The contribution of several nongovernmental organizations involved in the management of specific pathologies such as sickle cell disease is very significant and constitutes a major support, especially for the most deprived populations. The action is perceptible not only in the DR Congo but also in other countries of sub-Saharan Africa [8]. But these efforts remain insignificant compared to the magnitude of the disease, and a country's health policy cannot be based on impulses that are difficult to predict.

The second way is the frequent use of donated second-hand equipment to reduce the costs they (the equipment) represent in the health-care chain. This resource can make a great contribution if best practices for donors and donors' applicants are rigorously observed [9]. Unfortunately, very often this is not the case. Many donations still arrive in Africa without observing the prerequisites, which very often makes them either ineffective or unusable. On the other hand, recourse to donations of second-hand equipment should remain ad hoc, without becoming structural.

The third way is that of optimizing the use of the means available to approach the objectives set. At the international level, donors have understood the challenge of structured and well-executed health financing. This obliges the partners to accompany for decades the countries receiving aid through specific national programs in order to reduce deficits and achieve the objectives.

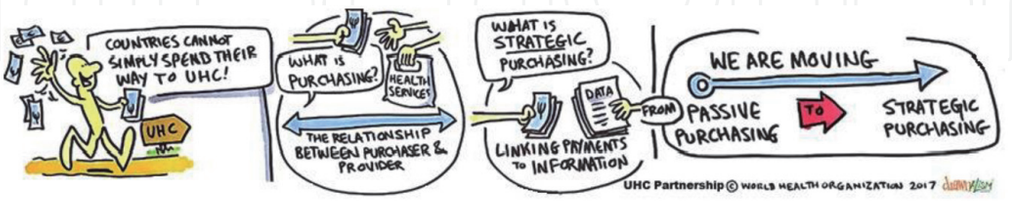
In the DR Congo, it is through the national health development program that the government and its partners express their willingness to provide effective and realistic solutions to the health problems of the DR Congo's populations. This is generally applied for a period of 5 years, iteratively after evaluation.

The partners in the health field remain practically the same for African countries, and their health problems are very similar: the fight against epidemics, malnutrition, and hereditary diseases. This probably explains why almost all countries in sub-Saharan Africa each develop a national health development plan, with virtually the same content except for a few differences. Examples include the DR Congo, Mali, Côte d'Ivoire, Burkina Faso, Benin, and Kenya. Therefore the methods applied by the partners for health support to the different countries will be very similar.

In the national health development plans drawn up in many sub-Saharan African countries since 2000 to date, the improvement of infrastructures and the strengthening of the capacities of the medical technical platforms, including the expression of

needs, acquisition, and maintenance of the systems acquired, are among the issues addressed. These topics involve a lot of money that will have to be put to good use; otherwise they can be a source of conscious or unconscious waste of scarce resources.

In the case of the DR Congo, a reflection carried out on the medical technical platform shows that the objectives assigned to medical infrastructure and equipment through national programs are never achieved and the situation is getting more complicated every year. And yet, after evaluation, the same programs continue with the same objectives and use practically the same methods [10]. In order to minimize procurement costs, the WHO proposes a strategic procurement approach to achieve universal health coverage [11]. The illustration below is more explicit.



This diagram raises fundamental questions that need to be answered if we are to succeed in our efforts. Indeed, countries cannot simply spend their money on universal health coverage. They must master purchasing, define the relationships between suppliers and buyers, define a purchasing strategy on the basis of useful data before disbursement, and finally move from passive purchasing to strategic purchasing.

The fourth path, a corollary to the third, consists of mobilizing and structuring human skills, each in its own sector, to boost the strategic purchasing process. Since the problem of strategic purchasing concerns all sectors, what can the biomedical engineer's contribution be as far as it is concerned?

From this point of view, the biomedical engineer can play an important role as a technical interface between the hospital, suppliers, and industry to make the right choices, as he is considered responsible for the research and development, architecture, selection, management, and safe use of all types of medical devices including single-use, reusable, prosthetic, implantable, and bionic devices, among others [12].

For several decades, a developed country like France has been efficiently involving biomedical engineers in the medical equipment procurement process [13]. It organizes hospital purchasing, where biomedical engineers play a leading role in the purchasing function that has developed in companies over the last 30 years or so [14]. Better still, it is developing a purchasing policy that, among other things, brings together the skills of biomedical engineers to offer end customer equipment negotiated at attractive prices through group purchasing [15].

But in the Democratic Republic of the Congo in particular and in sub-Saharan Africa in general, the biomedical engineering component does not seem to be sufficiently integrated at its best in the administrative and technical response mechanisms for improving health care. This aspect of things can only lead to a waste of funds when the actors at this stage do not master the equipment.

3. Situation of medical equipment dedicated to the analysis of hemoglobinopathies

In the field there are currently different types of electrophoresis equipment. However, to date, it is difficult to determine their number, origins, and brands,

given the country's size, diverse supply methods, and ineffective control mechanisms. Nevertheless, some facilities stand out from the others in terms of their number, mainly for historical and geographical, economic, and commercial reasons.

Historically and geographically, sickle cell disease was first discovered in black populations in Africa and in the Arabian Peninsula; to date it remains more frequent in these geographical areas. Initially, this disease, which later turned out to be hereditary, did not directly affect the Indo-European populations.

However, due to massive immigration, countries with well-organized prevention programs are now faced with the problems of uninformed couples of allochthonous origin, as well as variations in specific population characteristics, which is rare among indigenous populations [16].

In the early 1970s, screening tests were launched in the United States, and the American population of African origin was indeed very affected. In 1981, an experimental neonatal screening program began in the French Antilles and metropolitan France. It is set up by the Association Française pour le Dépistage et la Prévention du Handicap (AFDPHE). It was only in 2000 that neonatal screening for sickle cell disease was, this time, extended in whole France [17].

As a result of the above, electrophoresis systems are initially more equipped with routine programs dedicated to serum protein analysis; programs for the analysis of hemoglobinopathies will gradually come into operation. Indeed, the implementation of new programs involves significant costs that the manufacturer cannot incur without a guaranteed return on investment.

Since the greatest need for sickle cell disease management is in Africa, countries with strong historical ties to the continent will find it easier to sell their technologies to this potential market. Among them we will mention the most prominent firms such as HELENA, TITAN, BECKMAN SEBIA, and BIORAD.

In financial terms, the choice of equipment for routine needs will focus more on technical solutions that offer good results at lower cost. From this point of view, for the analysis of hemoglobinopathies, there is an established correlation between agarose gel electrophoresis on the one hand and capillary electrophoresis on the other [18]. On the other hand, high-performance liquid chromatography (HPLC) and capillary techniques are complementary and can be used routinely, knowing that capillary diagrams are easier to read and interpret than those obtained in HPLC. Even better, the development of the capillary technique for the characterization of hemoglobin variants suggested that it would become the first method of choice for screening in many clinical laboratories [19].

This trend is confirmed with regular innovations from certain manufacturers, and this is the case of SEBIA, which has added to its range for the screening of hemoglobinopathies [20]. In addition, the capillary technique is more sensitive than the HPLC technique for the detection of certain variants such as hemoglobin New York [21].

On the commercial level, thanks to their historical links with Africa, the first companies are more easily organized and set up local representations of their firms to facilitate the sale of their products. Among the first to obtain country-level representation are HELENA and BECKMAN.

But for almost two decades, we have been observing the rise of the SEBIA company, which offers different models of equipment according to the needs and which regularly innovates its products. Today, this firm, now a world leader in the field of electrophoresis, is among those with a large number of distributors in Africa.

Apart from the abovementioned brands, it is worth noting a slow penetration of products of Asian origin in the field. However, while the financial offer is attractive, distribution is still struggling to be structured in terms of regularity, reliability, and operation.

In the present case of the management of sickle cell disease and in order to make his contribution relevant and effective, the biomedical engineer must make an inventory of the existing situation in the field, evaluate the technologies in the state of the art, and propose material solutions that present a better compromise between technical and technological contributions and optimization of the financial aspect.

4. Analysis of onboard techniques on electrophoresis systems

The following theories are drawn mainly from the book *Appliances and Methods in Biochemistry and Molecular Biology*, whose pedagogical approach seems clearer.

4.1 General principles of electrophoresis

Electrophoresis has established itself over time as the method of choice for the qualification and quantification of different fractions in the management of hemoglobinopathy. It involves methods often embedded in laboratory materials. We review below the most common methods in electrophoresis of hemoglobin.

4.1.1 Definitions

Electrophoresis is a physical method of separating molecules based on their difference in mobility, under the effect of an electric field. Zone electrophoresis, carried out on a solid support, is used to essentially separate the ionizable biological macromolecules, that is to say proteins, nucleic acids, and certain polyosides and proteoglycans.

Liquid vein electrophoresis, currently capillary electrophoresis, is also applied to small molecules, organic or mineral, and not necessarily ionizable. In the most common case, the movement of the molecule depends on several intrinsic (due to the molecule itself) and extrinsic parameters, in particular linked to migration buffers which play the role of solvent [22].

4.1.2 Zone electrophoresis

This is the electrophoresis whose migration medium is stabilized by a real or sometimes virtual porous support as in the density gradient. In the case of a porous substrate, it is soaked with a buffer solution that both ensures conductivity and stabilizes the pH at the desired value. The molecules separate according to their different mobility in the system (they appear as migration zones) and will be visualized in a second time ("revelations"); we can even isolate them from the support for the preparatory purpose.

Zone electrophoresis is mainly applied to the separation of macromolecules.

4.1.2.1 Characteristics

These electrophoreses are often characterized by strong electroosmotic currents and sometimes intense Joule effect. The most common electroosmotic current is the electroendosmosis current, especially in polyosidic supports used at pH alkaline: the walls are negatively ionized as the macromolecules to be separated; positive buffer charges are attracted to the cathode and create a current that is in the opposite direction of electrophoretic migration.

Another electroosmosis phenomenon is related to the structure of the support, which can be assimilated to a capillary network; the friction forces are greater on the

edges of the support, and the center moves faster, distorting the migration band. Finally, the Joule effect heats the substrate and therefore evaporates the solvent; this is gradually replaced by the liquid of the vessels which rises in the support by capillary action, opposite both ends of the support, and annulling in the middle [23].

4.1.2.2 Supports

The supports must be chemically inert (low adsorbent) and homogeneous (regular microporous structure), have good mechanical resistance (handling), and possibly allow densitometric reading [24].

4.1.2.2.1 Paper

Paper is a natural cellulose; it is no longer used much because it is not homogeneous. Paper electrophoresis provides a strong electroendosmosis current and is a source of parasitic adsorptions (added chromatography), resulting in poor resolution; the Joule effect is important with heating, evaporation, and even electrolysis of the buffer. At high pressure (1000–3000 V), paper electrophoresis is mainly used to separate peptides and amino acids.

4.1.2.2.2 Cellulose acetate

Cellulose acetate is much more homogeneous than paper; this support allows densitometric reading, but the electroendosmosis current remains high. The applications of cellulose acetate are mainly found in medical biology, allowing a quantitative densitometric reading of the protein fractions rather roughly separated (plasma and urinary proteins, lipoproteins, and hemoglobins), or finer (isoenzymes), applying the potential gradients of the order of 30 V cm^{-1}. Resolution is poor, and reproducibility is average.

However, at alkaline pH (typically pH 8.6), Hb A2, Hb C, Hb E, and Hb O migrate to the same area, and Hb S, Hb D, and Hb G migrate at the same rate. In the case of suspicions of such hemoglobin abnormalities, an additional technique should therefore be considered [25].

4.1.2.2.3 Starch gel (cross-linked starch)

Starch gel is a polyoside; electrophoresis on this gel allows the separation of complex or heterogeneous oligomeric protein associations. Starch gel is little used because it is opaque, fragile, and not very reproducible.

4.1.2.2.4 Agarose gel

Agarose is desulfonated agar (purified agar); removal of sulfonates greatly limits the flow of electroendosmosis; agarose gels between 0.5 and 2% are not very viscous. They make it possible to carry out native electrophoresis as with the previous supports, that is, without denaturation of the macromolecules. Potential gradients up to 50 V cm^{-1} are usable for protein separation; agarose gel is gradually replacing cellulose acetate in most biomedical applications because agarose improves resolution and remains colorless, allowing a good densitometric reading. The agarose gel is also very homogeneous, thus ensuring good reproducibility, and is well adapted to zymographic reading [23].

The distinction between the different variants Hb A2, Hb C, Hb E, and Hb O, as well as Hb S, Hb D, and Hb G, is most often made by electrophoresis on agarose gel

at acidic pH (pH 6.0), which allows to separate Hb C, from Hb E and Hb O, as well as Hb S, from Hb D and Hb G. On the other hand, Hb E and Hb O, as well as Hb D and G, still cannot be differentiated by combining these two electrophoretic methods (cellulose acetate, agarose gel). In addition, these techniques have the disadvantage of consuming time and labor.

In addition, they lack precision for the quantification of hemoglobin in low concentrations, such as Hb A2, and for the detection of fast-migrating variants, such as Hb H or Hb Bart's. It is even now accepted that the quantification of variants by densitometry lacks precision and that these two electrophoresis techniques must be used for qualitative purposes. They are therefore most often used today in combination with another method, mainly high-performance liquid chromatography, which has a much higher accuracy.

A 1999 study by the College of American Pathologists showed a coefficient of variation (CV) of 33.6% for the quantification of Hb A2 at a concentration of 2.41% by densitometry from electrophoretic gels. By HPLC, the CV was 4.3% for Hb A2 at a concentration of 3.47%. Thus, the combination of these electrophoresis techniques with HPLC allows the identification and quantification of hemoglobin, the latter being performed by HPLC only [26].

4.1.2.2.5 Polyacrylamide

It is a polymer of acrylamide and N,N′-methylene-bisacrylamide (Bis), the acrylamide gel polymerization being obtained in the presence of a catalyst (ammonium persulfate) and a cross-linking agent (N,N,N′,N′-tetramethyl-ethylenediamine [TEMED]). The porosity of gels can be very precise; it depends on the relative concentrations of acrylamide and Bis.

The polymer obtained is very hydrophilic although insoluble in water and easy to mold even under small thicknesses (<1 mm); it is thermostable, not fragile, transparent, and inert chemically. There is almost no electroendosmosis flow and no macromolecules are absorbed. The resolutive power is generally superior to that of polyosidic gels using gradients of similar potential. The main disadvantage is that the acrylamide in solution is neurotoxic but also that the resulting porosities are very poorly adapted to very large molecules [27].

4.1.2.3 Zone electrophoresis methods

4.1.2.3.1 Native electrophoresis (without denaturation)

It is made on paper, starch, cellulose acetate, agarose gel, and sometimes polyacrylamide whenever we do not want to touch the tertiary and quaternary structures of macromolecules, thus their biological activities. This method without denaturation is a priori applicable to all types of macromolecules, both in vertical and horizontal tanks [27].

4.1.2.3.2 Isoelectrofocusing

Isoelectrofocusing, carried out on agarose gel or polyacrylamide gel, separates hemoglobin in a pH gradient according to their isoelectric point. To do this, ampholytes are introduced into the gel in order to create a continuous pH gradient under the effect of an electric field. The different hemoglobins contained in the sample to be analyzed will migrate to the region where the pH is equal to their isoelectric pH. At this position, the net load is zero, and the hemoglobin ceases to migrate and focuses into a narrow band.

This technique, capable of separating hemoglobin variants with isoelectric points different from 0.02 pH units, has excellent resolution and is very useful for detecting abnormal hemoglobin in the newborn. In fact, it allows a good separation of hemoglobins F, A, and S. Moreover, the electrical isofocusing is perfectly adapted to the analysis of large series. On the other hand, the main limitations of this method are a long and complex implementation. Therefore, its use is almost reserved for neonatal screening of hemoglobinopathies [28, 29].

4.1.3 Liquid vein electrophoresis

4.1.3.1 Characteristics

Typically, capillary electrophoresis is performed in a fused silica capillary coated with a polyamide layer of 20–200 μm of internal diameter and 20–200 cm of length. The capillary, placed in a thermostatization system, is filled with a buffer solution and plunges into two tanks containing the same solution. Each tank is connected to an electrode connected to a current generator. A large potential difference (several thousand volts) is applied to the terminals of each capillary to separate the molecules on the basis of their charge/mass ratio [30].

The use of a capillary has a double advantage: increases the sensitivity of the detection since a reading window in the capillary allows an absorbance reading with a very small optical path and increases the resolution by applying the potential difference of more than 10,000 V since it is easy to regulate the capillary in temperature [31].

4.1.3.2 Support

In this method, the buffer solution in contact with the two tanks of the system constitutes the support. Since liquid has no specific form, the buffer uses the capillary as a solid support, contributing also to electroendosmosis current production.

4.1.3.3 Liquid vein electrophoresis methods

There are several methods used in capillary electrophoresis including capillary zone electrophoresis (CZE), capillary gel electrophoresis (CGE), and micellar electrokinetic chromatography (MECC) [32]. In this study, we will limit ourselves to capillary zone electrophoresis which is the most exploited for hemoglobinopathy.

This method can be performed on a single-fused silica capillary in which an electroosmotic flux develops. It causes the negative molecules to the cathode where the detection is carried out, the injection being anodic.

The electroosmotic flux depends on the temperature, the ionic force, and the concentration of organic solvent.

4.2 Facilities

We will limit ourselves here to the most common routine techniques for the analysis of hemoglobinopathies in the Democratic Republic of the Congo in particular and in sub-Saharan Africa in general. They are often affected by accessibility during acquisition, ease of commissioning, operation, maintenance and supply, and cost.

On one side, our analysis is based globally on equipment meeting international standards such as ISO, FDA, and CE certification. Field experience shows that such

equipment can operate for about 7 years, if the manufacturer's operating recommendations are followed.

On the other hand, high-performance liquid chromatography has been developed to allow both the detection and confirmation of hemoglobinopathy in newborns with high sensitivity and specificity. In fact, its good sensitivity to the major variants involved in pathology and its speed of completion (about 3 min per sample), allowing the analysis of a large number of samples, have made HPLC a particularly suitable method for screening for hemoglobin abnormalities [33].

However, we will not discuss this technique in this study because, since its performance is comparable to that of the HPLC method, capillary electrophoresis quickly became the method of choice, just like HPLC, for the study of hemoglobinopathy. In addition, it is of economic interest: although the material cost is comparable to that of the HPLC, the expenditures on reagents are much lower. Indeed, the price of a capillary is much lower than that of a chromatography column, and the volumes of buffer used are much lower, about 1000 times less [34].

4.2.1 Manual systems

4.2.1.1 Offer

Manual systems for native electrophoresis (on cellulose acetate and agarose gel) or isoelectrofocusing offer the best acquisition possibility both in terms of cost and operational constraints. Their limits both in the separation and in the identification of hemoglobin variants will be used for the routine forms to be specified by the customer (identification of the electrophoretic profile, identification of specific variants).

The coupling of these methods to the reading system (densitometers) makes it possible to quantify the separate variants. And from this point of view, agarose gel electrophoresis offers better performance than cellulose acetate. On the other hand, the reagents are in the form of combs which often require a minimum of seven samples. Such a constraint requires, for economic reasons, to launch the samples in series of seven, which requires a consequent sizing and proper holding wire.

4.2.1.2 Facilities

For native electrophoresis the system is usually composed of a current generator and a migration tank. For isoelectrofocusing, the system consists of a stabilized supply, an isoelectrofocusing, unit, and a circulating cryostat.

The devices typically contain conventional electronic parts and boards, used in the manufacture of power generators. These components are often not complex, and do not require advanced technical repair. In addition, it has been found that when equipment actually meets ISO, FDA, or CE marking standards, it works well and lasts for a long time.

4.2.1.3 Use

These systems can be used in very small laboratories, without large volume flow of samples, for the screening of hemoglobinopathies, by planning a periodic operation. Indeed, the pre-analytical phase requires a lot of sample preparation time and immobilizes the staff for quite a long time. They can also be used in medium laboratories as a backup system.

The isoelectrofocusing system will be more targeted for newborn screening because it allows for a good separation of the Hb F, Hb A, and Hb S fractions, which assumes that the system is usually installed near a maternity ward.

4.2.2 Semiautomatic systems

4.2.2.1 Offer

Semiautomatic systems for native electrophoresis on cellulose acetate or agarose gel offer the possibility of processing large series of samples. Although the cost of the system is still high for a large number of health facilities, the manual routine is clearly improved. Semiautomatic systems (on cellulose acetate or agarose gel) are embedded on compact systems generally comprising a migration and coloring modules, which considerably reduce user handling.

The reading system, often equipped with advanced post-processing software, can be incorporated or remote. Nevertheless, the results obtained show the same limits as in the case of manual methods because the operating principles of the migration and coloring units taken separately are the same as those of the manual system.

4.2.2.2 Facilities

The semiautomatic system is generally composed of a compact unit comprising a thermoregulated migration module connected to a current generator and a fluidic module for coloring migrated gels. Technologically, an intelligent electronic unit manages the high voltage of the migration module, the fluidics of the coloring module, and the application programs for the two modules.

Generally, devices typically contain conventional electronic parts and boards. The process control is often ensured by position and temperature sensors. As their complexity is not great, maintenance can be easily carried out by a duly trained biomedical technician.

4.2.2.3 Use

These systems can equip medium-sized laboratories by planning either periodic operation or continuous operation, depending on the flow of samples. They are fairly widespread in the private laboratories which can obtain them and some public hospital laboratories often on behalf of specific programs. User maintenance monitoring must be ensured to guarantee proper functioning, and periodic annual maintenance must be carried out, insured in accordance with the manufacturer's recommendations.

4.2.3 Automatic techniques

4.2.3.1 Offer

Automatic techniques (only capillary zone electrophoresis) are the best offer, both in terms of flexibility of use and technical performance. Prices are still very high for many customers in Africa. Nevertheless, a good expression of needs and an adequate exploitation planning can allow a return on investment in an acceptable time.

4.2.3.2 Facilities

These techniques are carried out on compact systems, generally comprising capillaries at the ends plunging into reservoirs of buffer solution, themselves connected to the current generator. The apparatus also includes a detection system, most often a UV–visible spectrophotometer, linked to the wavelength of specific absorption of hemoglobin at 415 nm.

Migration support	Advantages	Disadvantages	Systems	Materials	Maintenance level	Constraints	Average cost (€)
Paper	- Native electrophoresis - Separation of amino acids and peptides	- High electroendosmosis current - Significant Joule effect - Bad resolution - Poor homogeneity - Parasite adsorptions	Manual	- Current generator	- Low	Good grounding	
				- Migration tank	- Free	Free	7000
				- Densitometer	- Low	Free	
Cellulose acetate	- Native electrophoresis - More homogeneous than paper - Separation of plasma and urine proteins, lipoproteins, hemoglobin, and isoenzymes	- High electroendosmosis currents - Poor resolution - Medium reproducibility - The hemoglobins A2, C, E, and O migrate in the same zone - The hemoglobins S, D, and G migrate at the same rate - Long implementation	Manual	- Current generator	- Low	Good grounding	
				- Migration tank	- Free	Free	7000
				- Densitometer	- Low	Free	
			Semiautomatic	- Compact staining and migration module and densitometer (integrated or no)	- Medium - Medium	- Steady voltage - Good grounding - Air-conditioned room - Inverter	15,000
Agarose gel	-Native electrophoresis - Nonnative electrophoresis - Limited electroendosmosis flow - Improved resolution - Very homogeneous - Separation of Hb C from Hb E and Hb O - Separation of Hb S from Hb D and Hb G	- No separation between HB E and Hb O - No separation between Hb D and Hb G - Inaccurate for the quantification of hemoglobin with low concentration (Hb A2) and for the detection of variants with fast migration (Hb H and Hb Bart's) - Long Implementation	Manual	- Current generator	-Low	Good grounding	
				- Migration tank	-Free	Free	7000
				- Densitometer	- Low	Free	
			Semiautomatic	- Compact staining and migration module and densitometer (integrated or no)	- Medium - Medium	- Steady stable - Good grounding - Air-conditioned room - Inverter	15,000

Migration support	Advantages	Disadvantages	Systems	Materials	Maintenance level	Constraints	Average cost (€)
			Semiautomatic	-Isoelectrofocusing module	- Medium	- Steady voltage - Good grounding - Air-conditioned room - Inverter	150,000
				-Circulation cryostat	- Medium	- Steady voltage - Good grounding - Air-conditioned room - Inverter	
Liquid vein (capillaries)	- Fast - Precise quantification of hemoglobin fractions - Flexible (small and large series)	-High water quality -Demanding environment	Automatic	- Compact migration and detection module	- High	- Steady voltage - Good grounding - Air-conditioned room - Inverter - Water quality	30,000

Table 1.
Summary table of different devices.

More sophisticated technology includes a capillary thermoregulation system, a control system comprising various sensors that manage optics, robotics, pneumatics, and detection, and a set of intelligent electronic cards capable of communicating with each other. Unlike previous methods, this method allows both to launch samples in an emergency without restriction and to process large series of samples.

In view of the complexity of its technology, management requires competent personnel who are regularly trained by the manufacturer. Water quality and user maintenance of equipment are of paramount importance to ensure the quality of results. This assumes that the supplier provides user training for the best care.

4.2.3.3 Use

Thanks to their flexibility in the work organization, these automated systems can equip laboratories with small volumes of samples, as well as those which process large volumes. Indeed, there are small and large models of automata to cover all these needs. Because of their high prices, these automata are acquired in public hospitals on the basis of research projects and specific programs. Private clinics acquire them for routine because of their performance. However they do have a few requirements that must be observed: the operating environment must be less dusty, the quality of electricity flawless, the quality of pure water, and regular maintenance.

We present in **Table 1** a summary of different devices that we have reviewed.

5. Discussion on the choice to be made for equipment acquisition

For better use of data in **Table 1**, it will be broken down below with two subsidiaries: **Tables 2** and **3**.

The information contained in **Table 2** will highlight the performance of the equipment according to different migration or embedded media available, while those in **Table 3** will compare the systems sold compared to hardware, installation constraints, execution time, and cost.

A cursory reading shows that the most efficient migration support remains one of the capillary methods (liquid vein): this support brings in itself the best return for the resolution, reproducibility, discrimination, and quantification, while the parasitic effects are almost nonexistent. But medical needs and health goals differ from one level to another and do not require in all cases the acquisition of such technology.

For routine screening for sickle cell disease, for example, the performance of migration on cellulose acetate amply suffices needs. This assumes that the precise separation variants like Hb A2, Hb C, Hb E, and Hb O are not a need first. On the other hand, as part of the requirements to cover, the effective separation of Hb S and Hb C variant is needed, and migration on agarose gel will best meet this requirement.

If, during treatment, abnormal forms of hemoglobin are associated, then the choice of medium will be directed towards agarose gel for a qualitative indication or the liquid vein for a quantitative indication of Hb A2. Indeed, abnormally low Hb A and abnormally high Hb A2 correlate with the presence of some abnormal forms of hemoglobin (alpha or beta thalassemia, etc.).

If precise separation and precise quantification of the variants Hb A2, Hb C, Hb E, and Hb O are required, then the liquid vein (capillary) support should be readily chosen.

Depending on work previously defined criteria, this table can guide the choice of performance basis based migration media.

But the only performance criteria are not sufficient to make a choice of appropriate materials. It will also take into account industrial supply in terms of existing

Performances	Migration support			
	Paper	**Cellulose acetate**	**Agarose gel**	**Liquid vein**
Nonnative electrophoresis			✓	✓
Native electrophoresis	✓	✓	✓	✓
Separation of amino acids and peptides	✓	✓	✓	✓
Homogeneity	✓ (poor)	✓ (medium)	✓ (good)	✓
Separation of plasma and urine proteins, lipoproteins, hemoglobin, and isoenzymes	—	✓	✓	✓
Resolution	✓ (bad)	✓ (poor)	✓	✓
Separation of Hb A2 from Hb C, Hb E, and Hb O	—	x (migrate in the same area)	✓	✓
Separation of Hb C from Hb E and Hb O	—	x	✓	✓
Separation of Hb S and Hb from Hb D and G	—	x (migrate at the same rate)	✓	✓
Separation of Hb S and Hb O	—	x	x	✓
Separation of Hb D and Hb G	—	x	x	✓
Rapidity	Low	Good	Good	Fast
Quantification of hemoglobin with low concentration (Hb A2)	—	x	x	✓
Detection of fast-migrating variants (Hb H, Hb Bart's)	—	x	x	✓
Precise quantification of hemoglobin fractions	—	x	x	✓
Flexible (small and wide series)	—	x	x	✓
Electroendosmosis current	Very high	High	High	High
Joule effect	✓	—	—	—
Pest adsorption	✓	x	x	x
Reproducibility	—	✓ (medium)	✓	✓
Water quality	Normal	Normal	Normal	High
Demanding environment	Normal	Normal	Normal	High

Table 2.
Performance comparison based on migration support.

systems, the materials that make up, their costs, and maintenance requirements. Below we provide a table that can guide us in assessing the choices to be made.

The line "migration support" is added in order to link **Tables 2** and **3**.

The analysis of the table shows that as the system moves from manual to fully automated, the necessary hardware is gradually being integrated into a compact module. From this point of view, this development provides an appreciable response to the ergonomic problems that are becoming very frequent in laboratories.

On the other hand, we observe that the installation constraints are more demanding when the analysis module becomes more compact. Indeed, in addition to the quality of the electrical ground line and voltage which greatly affect the operation of systems provided, the environment requires better temperature control (air conditioning), for example, besides the requirements of the water quality.

	Systems		
	Manual	**Semiautomatic**	**Automatic**
Migration support	-Paper -Cellulose acetate -Agarose gel	Cellulose acetate -Agarose gel	-Vein liquid (capillaries)
Equipment	-Power generator -Tank migration -Densitometer	-Module staining and migration -Densitometer (integrated or not)	-Module compact migration and detection
Installation constraints	-Quality ground line -Quality voltage	-Quality ground line -Quality voltage -Quality air conditioning	-Quality ground line -Quality voltage -Quality air conditioning -Quality of water
Execution time	Très long	Long	Court
Acquisition cost (en €)	7000	15,000	3000
Maintenance level	Bas	Moyen	Haut

Table 3.
Comparison of systems in terms of hardware, installation constraints, acquisition cost, and maintenance level.

The time required to perform the analyses is a very important parameter in the choice of equipment. On the one hand, it allows better management of the patient queue, and on the other hand, it ensures the management of reagents and consumables with a limited life. When the volume of samples to be treated in a routine manner is small, manual systems are suitable for both patient satisfaction and reactive management. If the volume of samples to be processed requires more than 1 day of work, the semiautomated system should be considered to resolve the queue. Finally, if the volume of samples increases further, the fully automated system will better meet expectations.

The management of reagents in the laboratory depends heavily on two important parameters that should be noted: this is the expiry date and the stability time after opening of the reagent. The expiry date indicated on the label is usually the date after which the manufacturer no longer guarantees the validity of the results, while the stability time after opening of the reagent indicates the period after which the manufacturer no longer guarantees its reliability after the first use.

Since the stability time is shorter than the expiry date itself, it will be necessary to ensure that each open reagent is consumed before that time. For example, the use of a reagent that has a stability time of 60 days and can analyze 1000 samples in a laboratory that receives only 10 samples per day is a waste. The use of this reagent before maturity requires an average daily rate of 20 samples, considering that the laboratory operates 6 days a week. Ten samples/day instead of 20 samples/day will theoretically cause the damage of half the reagent.

The level of maintenance, and in turn cost, follows the same trend: more compact system is provided and the higher level of maintenance.

Since the cost of acquiring systems increases with the complexity of the technology, it is important to ask good questions, find good answers, and make good choices based on real needs, to achieve savings. As an example, is it necessary to acquire a semiautomatic agarose gel system when, taking into account the medical needs and the volume of samples to be treated, the manual system on agarose gel support gives us satisfaction? Affirmative answer incurs an additional a

non-justified expenditure of 8000€. Worse still, such equipment oversizing compromises a substantial depreciation because it will be under-utilized.

6. Conclusion

The management of any pathology implies the appropriate choice of techniques and technologies. Indeed, beyond the medical needs that are priority, a control equipment acquisition cost is one of the major parameters providing effective support to strategies put in place.

Very often in sub-Saharan countries, the aspect of the consequent acquisition of the necessary technology is not always thorough, and this can lead a poor quality of reported results, the inaccessible test cost for the poorest people, and the delicate operation of projects being implemented.

The choice of equipment performed after an objective needs analysis enables to optimize the process of acquiring, to ensure the quality of reported results, and to provide more accessible costs to target populations generally poor.

According to WHO recommendations, technology assessment, device evaluation, needs planning, selection and acquisition, installation, commissioning, and finally monitoring should be part of a successful acquisition procedure [35].

Such an approach should involve all stakeholders, namely, doctors, managers, biomedical engineers, and users.

In the case of sickle cell anemia, the inventory of installed park shows that beside manual methods, diagnostic techniques most common in the Democratic Republic of the Congo and even in sub-Saharan Africa are phenotypic techniques. These include *the electrophoresis at different pH, the isoelectrofocusing, the capillary electrophoresis, and the high-pressure liquid chromatography.* The first three mentioned are most used for their reliability, flexibility, ease of installation, and maintenance.

The prices of the equipment listed in the table remain indicative. We have taken into account only good-quality equipment commonly used in the DR Congo and by extension in other countries of sub-Saharan Africa.

For low-income countries, the costs of such facilities are still high overall. Indeed, the increase in health expenditure, which represents 10% of the world's gross domestic product (GDP), is faster than the growth of the world economy. According to a new World Health Organization report on global health spending, it is increasing rapidly, particularly in low- and middle-income countries, where spending is increasing at an average of 6% per year, compared to 4% in high-income countries.

Health expenditure is assumed by governments, by individuals who pay for their own care (out-of-pocket payments), and by other entities such as voluntary health insurance schemes, employer-sponsored schemes, and nongovernmental organizations. On average, 51% of a country's health expenditure is assumed by general government and more than 35% by individuals in the form of direct expenditure. One of the consequences of this situation is that every year 100 million people are plunged into extreme poverty [36].

For the countries concerned, the acquisition of these health technologies requires new upstream procurement strategies to meet acquisition and operating costs. And from this point of view, some developed countries such as France are now developing group procurement procedures in public hospitals.

According to a recent study conducted in the Democratic Republic of the Congo on an investment in capillary electrophoresis equipment for a project on sickle cell disease, this can contribute to improve quality and low cost of tests, if a complete analysis of needs is carried out upstream.

In this study, for an equipment activity extending over a period of 7 years, the cost of acquisition and maintenance cost represent, respectively, 11.4% and 5.0% of the total life cycle cost.

But when the activity of the same equipment is done over a period of 2 years, the cost of acquisition and maintenance cost represent, respectively, 31.0% and 3.9% of the total life cycle cost.

Added to this, for the same annual rate, the minimum unit test cost is € 3.9 for a 7-year activity cycle, whereas it costs € 5 if the activity cycle is reduced to 2 years [37].

Therefore, it should be noted that when operating conditions remain the same, amortization of equipment carried on shorter lead times significantly increases the cost of the test at the expense of patients.

Even though this example only concerns electrophoresis capillary equipment, extrapolating conclusions on agarose gel equipment is possible for the following reasons: installation, operation, and maintenance are less demanding than for capillary technology.

While sub-Saharan Africa is the most affected region in the world for sickle cell disease, research and care are relatively slow.

At its 60th session held in Malabo from 30 August to 3 September 2010, the WHO was already raising the option of a strategy for its African region. Nine years after the effects are hardly noticeable.

The management improvement of this pathology solicits several challenges, including the one concerning the technical platform necessary for diagnosis. The costs of acquiring and operating equipment often require significant fundraising, which is often lacking. The missing financial means are often one of the first obstacles to the launching of the relevant programs.

The study mentioned above proves that it is possible to optimize the available resources, however modest they may be, in order to obtain good and lasting results.

In the case of biomedical equipment, it is sufficient to involve the right people to achieve the expected results. Policymakers in sub-Saharan African countries must therefore integrate the skills of biomedical engineers into the design and start-up of medical projects so that they, in turn, contribute effectively to improve the quality of medical care populations.

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